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TECHNOLOGIES

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December 22, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

Re: Docket No. 97N-484S, "Suitability Determination for Donors of Human Cellular and Tissue-Based Products," 64 Fed. Reg. 52696 (Sept. 30, 1999)

Dear Sir or Madam:

Regeneration Technologies, Inc. (RTI) appreciates this opportunity to comment on the above-referenced Food and Drug Administration (FDA) Federal Register Notice. RTI distributes a variety of human tissue allografts from our processing facility in Alachua, Florida. Many of RTI's allografts are based upon the ways in which surgeons themselves have cut, shaped, and used allograft tissue in the operating room over the past several decades and up to the present. By distributing allografts that are processed under aseptic clean room conditions, and in accordance with current FDA donor screening and testing requirements, individual state requirements, and applicable voluntary standards of such organizations as the American Association of Tissue Banks, RTI strives to make it easier for surgeons to use allograft tissue to benefit patients.

RTI believes in the importance of appropriate donor screening and testing to minimize the risk of disease transmission. We are concerned, however, that certain parts of FDA's proposed donor screening and testing requirements are unnecessarily burdensome, and we believe that-certain aspects of the proposal need to be clarified. We also continue to be concerned about the "'jurisdictional" criteria that FDA has proposed to use in determining whether a tissue-based product will be regulated solely under the Public Health Service Act, or as a medical device or biologic drug under the Federal Food, Drug, and Cosmetic Act, and about the process by which FDA will make such determinations. Our specific comments are discussed below.

97N-484S

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I. Proposed "Jurisdictional" Criteria

In an earlier proposed rule, "Establishment Registration and Listing for Human Cellular and Tissue-Based Products," 63 Fed. Reg. 26744 (May 14, 1998), FDA proposed four criteria for determining whether a human cellular or tissue-based product should be regulated as a tissue solely under the Public Health Service Act (PHS Act), or as a drug or device under the Federal Food, Drug, and Cosmetic Act (FDC Act).' FDA has now incorporated these criteria (with certain modifications) into the current proposed rule for donor suitability and testing. Because the proposed criteria are not yet final, but are nevertheless incorporated in this proposal, RTI is providing comments on those items in addition to the provisions relating donor suitability.

It is our understanding that under FDA's proposed framework, for a tissue-based product to be regulated as tissue solely under the PHS Act, and not as a drug or device under the FDC Act, it must (1) be minimally manipulated; (2) not be promoted or labeled for any use other than a homologous use; (3) not be combined with or modified by the addition of any component that is a drug or device; and (4) not have a systemic effect unless it is for autologous use, family-related allogenic use, or reproductive use. 64 Fed. Reg. at 52720 (proposed 2 1 C.F.R. § 127 1.10). RTI continues to have reservations about the definitions of these criteria, We are also troubled by the way in which FDA already appears to be making jurisdictional decisions about tissue-based products by applying these proposed criteria.

FDA's proposed definition of "minimal manipulation" for structural tissue is "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement." 64 Fed. Reg. at 52700 (proposed 2 1 C.F.R. § 127 1.3(g). The proposed definition of "homologous use" means "the use of a . . . tissue-based product for replacement or supplementation and . . . [f]or structural tissue-based products, . . . when the tissue is used for the same basic function that it fulfils in its native state, in a location where such structural function normally occurs." Id. (proposed 21 C.F.R. § 127 1.3(d)(1)). In the proposed establishment registration rule the agency explained that in its view, "minimal manipulation" would include "separation of structural tissue into components whose relevant characteristics relating to reconstruction or repair are not altered, . . . extraction or separation of cells from structural tissue in which

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1 RTI submitted comments to FDA's proposed establishment registration rule on August 12, 1998. (Copy enclosed.)

the remaining structural tissue's relevant characteristics relating to reconstruction and repair remain unchanged, . . . [and] [c]utting, grinding, and shaping; soaking in antibiotic solution; sterilization by ethylene oxide treatment or irradiation; cell separation; lyophilization; cryopreservation; and freezing." 63 Fed. Reg. at 26748. "Homologous use" would include "bone allograft obtained from a long bone but labeled for use in a vertebra; skin allograft obtained from the arm but labeled for use as a skin graft on the face; pericardium, a structural membranous covering of the heart, labeled for use as a structural membranous covering for the brain. . . ." Id. at 26749.

One of the allografts that RTI distributes is the cortical bone dowel. On June 28, 1999, FDA announced a meeting of the Orthopaedic and Rehabilitation Devices Panel of the Medical Device Advisory Committee to consider "classification of bone dowel devices of human origin." 64 Fed. Reg. 34659. Notwithstanding that the proposed tissue criteria had not been finalized, prior to announcing the meeting, the agency provided the panel with a copy of the proposed establishment registration rule, and advised in a June 10, 1998 briefing memorandum that letters had been issued to tissue banks and device manufacturers stating that certain bone dowel products for use in lumbar spinal fusion surgery would not be regulated as human tissue, but as devices. The memorandum also stated that "[t]his decision was based on the amount and type of manipulation used to process the bone, as well as its ultimate non-homologous use, *i.e.*, within the disc space as a connector between two vertebrae. As a result, these devices would need to be classified." (Emphasis added.)

As RTI explained in a July 15, 1999 submission to the panel, we believe FDA cannot lawfully make jurisdictional decisions about tissue-based products based on the proposed criteria until the completion of notice-and-comment rulemaking, as required by the Administrative Procedure Act, 5 U.S.C. § 553. Although FDA ultimately postponed the panel's discussion of bone dowels, the fact that FDA had summarily decided that bone dowels were devices based on the application of proposed criteria, and without prior public notice, is alarming. RTI expects that there will be many other tissue-based products for which the interpretation and application of FDA's proposed criteria will present difficulty, and with respect to which FDA and industry will have different views. Due to the potential regulatory consequences of not meeting the criteria for regulation as tissue solely under the PHS Act (e.g., the requirements for data submission and premarket review), RTI urges FDA to provide more advanced notice of its thought-process, and to solicit public input when it evaluates tissue-based products under the criteria, before drawing conclusions as to how such products will be regulated.[2]

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[2] It further appears to RTI that the Tissue Reference Group (TRG) is now the principal

As for the substance of FDA's proposed criteria, regarding the "minimal manipulation" criterion, RTI submits that it is extremely difficult to draw a meaningful line of demarcation between the amount of cutting and shaping that will cause a structural tissue allograft to be regarded as "minimal processing" and the amount that will move that allograft over the line to "more than minimal processing." For example, no one is likely to contend that a whole femur is "more than minimally processed." But is it "more than minimal processing" to cut and distribute only an end, or the long mid-section of the femur? How about a shorter segment of the mid-section such as a one-inch ring? The same one-inch ring cut on the diagonal? The same one-inch ring with grooves? If a physician desires a triangular piece of fascia lata, or determines that saphenous vein allografts are easier to implant and heal faster if they have fringed rather than straight cut ends, do these pre-shaped allografts become devices? Drawing a rigid, arbitrary line could have significant regulatory consequences including inappropriate data submissions and labeling requirements for many types of widely-used structural tissue. Using an overly broad definition would also deter innovation, which would be contrary to FDA's objective in developing its tissue policy.

Concerning the "homologous use" criterion, RTI submits that there are uses for structural tissues, such as fascia lata, that have a long history of safe use in a variety of procedures which might be considered non-homologous under FDA's proposed definition. Premarket review would not make sense for structural tissue allografts with a long history of safe and effective non-homologous use – particularly considering the agency's stated objective not to impose unnecessary regulatory burdens. See 64 Fed. Reg. at 52697.

As for the criterion regarding the combination of tissue or cells with a component that is a drug or device, FDA's proposal to delete "nontissue or noncellular" from the definition does not resolve the questions RTI raised about this criterion in our comments on the establishment registration rule. Specifically, we remain concerned that this criterion

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agency body considering how tissue-based products should be regulated by FDA. Although the TRG already has made recommendations for a number of human cellular and tissue-based products, none of the specific recommendations have been publicly shared or announced. While we recognize that many cases may involve confidential information that cannot be disclosed, RTI submits that industry, the agency, and the tissue regulatory process in general would benefit from providing greater transparency into the process by which the TRG applies the criteria with respect to different products.

could result in arbitrary and unnecessary regulation of tissue and cellular products as drugs or devices. Many substances regulated by FDA may not affect the safety of a cellular or tissue product. RTI recommends that FDA not regulate a cellular or tissue product containing the component as a drug or device that would require premarket review unless it could affect recipient safety. RTI further believes that it should be the manufacturer who makes the initial determination of whether this threshold has been crossed.

II. Proposed Donor Suitability and Testing

A. Definitions of "Establishment" (proposed 21 C.F.R. § 1271.3(b)), "Manufacture" (proposed 21 C.F.R. § 1271.3(f)), and "Establishments Not Required to Comply" (proposed 21 C.F.R. § 1271.20)

In the proposed establishment registration rule, FDA proposed to define an "establishment" as

> a place of business under one management, at one general physical location, that engages in the manufacture of human cellular or tissue-based products. The term includes, among others, facilities that engage in contract manufacturing services for a manufacturer of human cellular or tissue-based products. The term also includes any individual, partnership, corporation, association, or other legal entity engaged in the manufacture of human cellular or tissue-based products, except that an individual engaged solely in the procurement or recovery of cells or tissues or under contract to a registered establishment is not required to independently register."

63 Fed. Reg. at 26754 (proposed 21 C.F.R. § 1271.3(b)) (emphasis added).[3] FDA proposed to define the term "manufacture" as including, but not limited to "any or all steps in the recovery, screening, testing, processing, storage, labeling, packaging, or distribution of any human cellular or tissue-based product." 63 Fed. Reg. at 26754 (proposed 21 C.F.R. § 1271.3(f)) (emphasis added).[4]

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[3] See also 64 Fed. Reg. at 52699-700.

[4] See also Id. at 52700.

RTI is concerned that these two definitions, when read in conjunction with the proposed establishment registration rule preamble discussion, could be interpreted to mean that individual sales representatives who distribute, but do not procure, recover or process tissue, are required to register as "establishments." On the other hand, the exception at the end of the "establishment" definition could also be interpreted to exclude individuals, including sales representatives, from the "establishment" definition if they are under contract to a registered establishment. FDA should clarify that the "under contract to" language can apply to other individuals contracting with the registered establishment, and not just to contractors engaged in the "procurement or recovery" of cellular or tissue-based products. RTI believes, for example, that individual sales representatives who distribute tissue under contract to a registered establishment should not be required to register with the agency as tissue establishments.

The proposed registration rule contained a provision describing the types of establishments that would not be required to comply with the registration and listing requirements. See 63 Fed. Reg. at 26754 (proposed 21 C.F.R. § 1271.20). In the proposed donor suitability rule, FDA has clarified that such establishments will be exempt from all of the requirements of part 1271, not just registration and listing. See 64 Fed. Reg. at 52699, 52720. The agency has also modified the language of the fourth exception so that it now applies to "[e]stablishments that do not recover, screen, test, process, label, package, or distribute, but only receive or store human cellular or tissue-based products solely for pending scheduled implantation, transplantation, infusion, or transfer within the same facility." 64 Fed. Reg. at 52720 (proposed 21 C.F.R. § 1271.20(d)).

RTI recognizes that FDA added the terms "recover, screen, test, process, label, package, or distribute" to clarify that the exception applies to "end-user" establishments as discussed in the preamble of the proposed establishment registration rule. See 63 Fed. Reg. at 26748. However, the question RTI presented in its comments on the proposed registration rule concerning the potentially narrow interpretation of this exception remains. RTI believes that this exception, as currently worded, could be interpreted as not applying to hospitals, surgery centers, or dental surgeons which order limited supplies of tissue without pending or scheduled surgery, thus subjecting these entities to all the requirements of a tissue bank. RTI does not believe that FDA intended this result based on the agency's preamble discussion of end-user establishments in the proposed establishment registration rule. However, an FDA official recently stated that if an establishment orders tissue for a non-pending or unscheduled procedure, the establishment would not be exempt from the requirements of Part 127 1. This interpretation would mean that hospitals, surgery centers and dental surgeons could not order and stock limited supplies of commonly-used tissue for unscheduled emergency purposes without registering and listing, and complying with the

other requirements. As a result, such entities may choose to discontinue stocking tissues for emergency use. This would impede the timing and/or appropriateness of patient care where tissue-based products represent the state-of-the-art. RTI submits that hospitals, surgery centers, and dental surgeons which stock limited supplies of tissue-based products not earmarked for use in pending, scheduled procedures should be exempt from the requirements of Part 127 1, and that FDA should clarify that such establishments are included within the scope of the exemption proposed in 21 C.F.R. § 1271.20(d).

B. Definition of "Relevant Medical Records" (proposed 21 C.F.R. § 1271,3(v))

FDA proposes to define the "relevant medical records" of tissue donors as "a collection of documents" that includes a current donor medical history interview; a current report of the physical assessment of a cadaveric donor or the physical examination of a living donor, and, if available, laboratory test results, medical records, coroner and autopsy reports, and records or other information from any source pertaining to risk factors, signs and symptoms, and treatments, for communicable diseases. 64 Fed. Reg. at 52719-720 (proposed 21 C.F.R. § 1271.3(v)). RTI agrees that it is important to have as much relevant information as possible about the donor to determine whether the donor is suitable. RTI strongly believes however that the scope of these medical records needs to be limited to that information pertaining to relevant communicable diseases. Appropriate donor screening is an essential step in ensuring a safe supply of tissue, however, the collection of data beyond the scope of what is relevant serves to undermine this purpose. Donor records should be concise, focusing only on those diseases deemed relevant. The proposed approach would increase the likelihood that a potentially significant finding will be lost in the minutiae.

A specific example of extraneous data collection is the proposed requirement of the receipt of finalized autopsy results prior to the release of donor tissue. Due to the limited number, the inherent variability in the scope and depth of examination and the relative insensitivity of such procedures at detecting a communicable disease as compared to current serological testing methodologies, autopsy results do not add significant value to the donor screening process. Additionally, certain tissue products having limited expiration dates (e.g., cartilage, skin, corneas), need to be released before coroner and autopsy reports become available. RTI recommends that FDA limits the scope of the required documentation to those records directly pertaining to communicable diseases.

C. Testing for Transmissible Spongiform Encephalopathies (proposed 21 C.F.R. § 1271.85(e))

FDA is proposing to require that donors of dura mater be assessed for evidence of transmissible spongiform encephalopathies (TSE). 64 Fed. Reg. at 52723 (proposed 21 C.F.R. § 1271.85(e)). As the agency notes in the proposal, however, there is currently no FDA-approved or validated test for screening TSE in brain tissue. Id. at 52706. Therefore, FDA proposes to require a full brain autopsy of the donor, including gross and histological examination by a qualified neuropathologist. Id. This method of screening is not feasible for at least two reasons. First, the cost of a full brain autopsy would be prohibitive. RTI has information to suggest that a single, full brain autopsy by a neuropathologist would cost upwards of $1,000. This will represent a significant increase in the cost of obtaining this tissue. Second, families of donors may be unwilling to permit full brain autopsies, thereby reducing the supply of available dura mater screened in accordance with FDA's requirements. Until there is an FDA-approved or validated test for TSE, RTI recommends that FDA permit dura processors to perform brain biopsies instead of full autopsies. RTI believes that brain biopsies are currently used by most processors of dura mater to screen for TSE.

D. Timing of Donor Specimen Collection (proposed 21 C.F.R. § 1271.80(b))

FDA proposes to require that specimens for donor testing be collected "at the time of recovery of cells or tissue . . . or within 48 hours after recovery." 64 Fed. Reg. 52722 (proposed 2 1 C.F.R. § 127 1.80(b)). In certain situations, with regard to living donors, FDA proposes that a testing specimen could be collected up to 7 days prior to recovery. Id. RTI submits that FDA's approach with respect to cadaveric donors is unnecessarily restrictive.

Patients who are admitted to the hospital, and who ultimately become donors, often have blood samples drawn upon admission, or arrival at the emergency room. Such patients may experience blood loss requiring the transfusion of blood and/or other fluids. Based on data collected at RTI, it does not appear that a dilution of 1:2 alters the results of serological testing. According to this data, dilutions greater than 1: 100 are necessary to change a positive serological result to a negative or significantly prolong the window period. Therefore, RTI urges FDA to reexamine the previously enacted criteria for significant hemodilution and allow individual firms to establish meaningful algorithms to guard against hemodilution based upon the most current and accurate scientific data. In lieu of a change in established hemodilution criteria, RTI suggests that for cadaveric donors, like living donors, FDA should permit specimens to be collected up to 7 days before death and recovery of donated tissue.

E. Requirement That Donor Suitability Determination Records Accompany Tissue-Based Products (proposed 21 C.F.R. § 1271.55)

FDA proposes to require that distributed tissue-based products be accompanied by documentation of donor suitability including, a copy of the donor's relevant medical records, results of required testing, and the name and address of the establishment that made the suitability determination. 64 Fed. Reg. at 52721 (proposed 21 C.F.R. § 1271.55(a)). In the alternative, FDA proposes that such products be accompanied by a "summary of records" defined as "a condensed version of the records of required screening and testing . . . contain[ing] (1) [a] statement that the communicable disease testing was performed by a laboratory . . . under the Clinical Laboratory Improvement Amendments of 1988 (CLIA); (2) [a] listing and interpretation of the results of all communicable disease tests performed; (3) [a] statement describing the types of records which may have been reviewed as part of the relevant medical records; and (4) [t]he name and address of the establishment determining the suitability of the donor cells or tissues." Id. at 52721, 52720 (proposed 21 C.F.R. § 1271.3(x)).

Requiring tissue establishments to supply copies of "relevant medical records" and reports of required testing (with all private identifying information removed) or even a "condensed version" of such records for each graft distributed would make the task of distributing allografts extremely cumbersome and more costly. The cost of packaging and shipping allografts alone would increase dramatically if records and reports must also be shipped. Moreover, "relevant medical records" for some donors may encompass thick folders of information. Tissue establishments would also need to carefully review all such records for identifying personal information, and delete that information before disclosure. While RTI supports the objective behind FDA's proposed record distribution requirement, we suggest that the agency modify its approach to eliminate these burdens. Specifically, we believe it would be sufficient to provide a statement whether the donor has been determined to be suitable or unsuitable, a checklist delineating the tests that were performed and whether those results were positive or negative, and the name and address of the establishment that made the suitability determination. We do not believe that tissue establishments should be required to provide actual copies of the records and results to end-users. Nor do we believe that the benefits of providing such information would be commensurate with the costs.

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RTI thanks the agency for this opportunity to comment on the proposed donor suitability requirements, and for its consideration of our views.

Respectfully submitted,

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Regeneration Technologies, Inc. (RTI) submits these comments on the above-referenced Food and Drug Administration (FDA) Federal Register notice.

RTI is a tissue processing and R&D facility that processes human tissue for implantation. RTI is located in Alachua, Florida where processing is performed in Class 100 or greater cleanroom suites.

Before addressing the proposed registration requirements, we wish to comment on certain aspects of the conceptual framework underlying FDA's proposal as described in the preamble. According to the proposed rule, whether a cellular or tissue-based product will be regulated under section 361 of the Public Health Service Act (PHS Act) or will also be subject to premarket review under section 35 1 of the PHS Act or the Federal Food, Drug, and Cosmetic Act (FDC Act) depends on whether the product adheres to certain criteria. FDA states that products combined with or modified by the addition of any 'nontissue or noncellular component that is a drug or device" will not be regulated as "36 1 products" but under PHS Act section 35 1 and/or the FDC Act as drugs, devices, or biologics subject to premarket review.

FDA's explanation of the "nontissue or noncellular component that is a drug *or* device" leaves open several questions. For example, would FDA regard a component as falling into this category based on its actual function in the product? Or is the determining factor how the component is already regulated by the agency? Will all products containing a "nontissue or noncellular component that is a drug or device" necessarily be subject to regulation and premarket review as drugs or devices?

In the case of demineralized bone (DMB) (which we believe FDA has correctly decided meets the "minimally manipulated" criterion), the proposal notes that DMB would be regulated as a "361 product" "provided it is used for a homologous function and is not combined with a noncellular or nontissue component that is a drug or device." FDA distinguishes that "bone combined with collagen or growth factors" would be outside the "361 category" and subject *to* regulation as a biological drug or device.

Considering that FDA regulates collagen as a device, and that it has previously required 5 1 *O(k)* premarket clearance for a product consisting of DMB and collagen, the position that "bone combined with collagen . . ." would not be in the "361 product" category appears to be consistent with past practice. However, FDA has permitted another product consisting of DMB and

glycerol (a drug) to be marketed without premarket review, as "banked human tissue." Under the proposal, would glycerol be a "noncellular or nontissue component that is a drug or device"? Would cellular and tissue products meeting the "361 product" criteria except for the addition of glycerol be regulated as a biologic drug or device and required to undergo premarket review?

RTI is concerned that blanket application of the "noncellular or nontissue component that is a drug or device criterion" would result in arbitrary and unnecessary regulation of tissue and cellular products as drugs or devices. Many substances regulated by FDA may not have any effect on the safety or viability of a cellular or tissue product, or make any materially significant contribution to its function. RTI submits that if the use of a component does not raise such issues, FDA should not regulate a cellular or tissue product containing the component as a drug or device, or require premarket review for the product. We would also caution the agency when applying this criterion to avoid imposing different and uneven requirements on similarly situated products.

An issue concerning the "homologous use" criterion is whether a product that does not meet the criterion in all cases must necessarily undergo premarket review. According to FDA's proposed definition for homologous use of structural tissue, "[h]omologous use . . . occurs when the tissue is used for the same basic structural function that it fulfills in its native state, in a location where such structural function normally occurs . . . [for example] when it is used to replace an analogous structural tissue . . . ." Some structural tissues, such as fascia lata, have been used safety and effectively for many years for a wide range of uses, Some of the uses could be regarded as nonhomologous under FDA's definition. We believe that premarket review would not make sense for a product with a long history of safe and effective nonhomologous use, especially in light of FDA's objective not to impose unnecessary regulatory burdens or restrictions.

One type of cellular product not mentioned in FDA's proposal which we believe would fall into the proposed "36 1 product" category is hepatocytes recovered from the human liver for transplantation into patients with liver failure. The procedure for recovering and processing hepatocytes for transplantation includes cell separation, cryopreservation, and freezing, all of which meet FDA's definition of "minimal manipulation." In addition, hepatocytes are intended for homologous use — specifically, replacement of lost liver function. Hepatocytes are not combined with a nontissue or noncellular component, and do not have a systemic effect.

Turning to the registration requirements, FDA proposes to require all establishments that engage in the manufacturer of human cellular or tissue-based products, whether such products are "361 products" or products subject to regulation as drugs or devices under PHS Act 351 or the FDC Act, to register and list their products under proposed Part 1271 within 5 days of beginning operations. Establishments would need to submit, among other information, "[a] signed and dated statement by the reporting official affirming that all information contained in the registration and listing form is true and accurate," a list of "all human cellular or tissue products . . . that are recovered, screened, tested, processed, stored, labeled, packaged, and distributed," and a "statement of whether each product meets the criteria set out in 1271.10."

We do not believe a statement affirming the truth and accuracy of the information contained in the registration and listing form is necessary. FDA does not require such a statement in the registration and listing regulations for drugs or devices. If the requirement is retained, a reporting official should be allowed to state that the information is true and accurate to the best of his or her knowledge. This would make sense for the scenario in which a reporting official

must rely on information from persons directly involved with the product because he or she does not personally know all the details.

In the proposal, the agency has stated "FDA must keep informed of the state of the industry, including developments such as the introduction of new products." It is unclear from this statement if the FDA would consider the introduction of a new size of an existing product to be a "new product" which would require under the proposed approach, notification prior to releasing this product. An example would be, the tissue bank has a product called fascia lata which is available in four sizes. 4cm x 8cm, 6cm x 10cm, 4cm x 12cm and 6cm x 14cm. After repeated request for a larger size, the tissue bank intends to add a product for fascia lata which will be 8cm 16cm. Would this addition require immediate notification, or would it only need to be noted on the next scheduled listing update?

FDA has stated "Once FDA has a complete list of the cell and tissue industry and its products," and "Definitions 1. Human Cellular or Tissue Based Product: A human cellular or tissue based product is defined.. . . as a product containing human cells or tissues,". It is clear that FDA intends for an establishment to list each of its products, but it is not clear if FDA is defining products as families of similar tissues or as each individual tissue. An example would be, tissue bank A manufactures cortical cancellous chips. The family group would be cortical cancellous chips, where as the individual tissues would be:

Cortical Cancellous Chips 10cc	Freeze Dried	Cortical Cancellous Chips 10cc	Frozen
Cortical Cancellous Chips 1 5cc	Freeze Dried	Cortical Cancellous Chips 15cc	Frozen
Cortical Cancellous Chips 20cc	Freeze Dried	Cortical ***Cancellous*** Chips 20cc	Frozen
Cortical Cancellous Chips 25cc	Freeze Dried	Cortical Cancellous Chips 25cc	Frozen
Cortical Cancellous Chips 30cc	Freeze Dried	Cortical Cancellous Chips 30cc	Frozen
Cortical Cancellous Chips 35cc	Freeze Dried	Cortical Cancellous Chips 35cc	Frozen
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Cortical Cancellous Chips 75cc	Freeze Dried	Cortical Cancellous Chips 75cc	Frozen
Cortical Cancellous Chips 80cc	Freeze Dried	Cortical Cancellous Chips 80cc	Frozen
Cortical Cancellous Chips 85cc	Freeze Dried	Cortical Cancellous Chips 85cc	Frozen
Cortical Cancellous Chips 90cc	Freeze Dried	Cortical Cancellous Chips 90cc	Frozen

To cloud the issue even further, each of the products listed above could also be provided irradiated doubling the number of individual products. Tissue bank B may manufacture the exact same products and list them as Cancellous Cortical Chips. Tissue bank C may also manufacture the exact same product and list them as Cancellous Chips with Cortical Chips or Cortical Chips with Cancellous Chips. For this reason, if the FDA has not considered listing by families, we would recommend this be incorporated into the FDA final rule. The example given above is only one, this will be repeated for many processed tissues, with the only difference between two tissues being millimeters. Individual product listing for a given tissue bank could be in the thousands,

FDA has stated in section 1271.25 (b) "that are recovered,. . ." . Recovered tissue(s) are not products until they have been processed. The FDA may want to consider having separate categories for tissue(s) recovered and tissue products.

FDA has stated that "changes in an establishment's ownership or location are to be submitted as an amendment to registration within 5 days of such changes." It is not clear from this statement if the FDA will include additional space or the addition of an adjacent building as a change in location. If a tissue bank, through expansion adds an additional building to their facility, which may be adjacent, but have a different address, would this be a new location?

FDA has stated in the Background section under "Exceptions", "Establishments that receive human cellular or tissue based products solely for implantation, transplantation, infusion, or transfer within the same facility do not come under the terms of part 1271. This exception is intended only for end-user establishments, that is, establishments that do not procure, distribute, or otherwise manufacture human cellular or tissue based products." In section 1271.20 (d), however, FDA states that the exception applies to: "Establishments that only receive or store human cellular or tissue based products solely for pending scheduled implantation, transplantation, infusion, or transfer within the same facility." This section has a narrower interpretation and could be interpreted to mean that any hospital, which orders tissue without having a scheduled surgery, would have to register. We do not believe this is the intention of the FDA as demonstrated in the background section. Many hospitals order tissues, which are in high demand and low availability knowing that they will be used in the near future. An example would be patella tendons used for anterior cruciate ligament repairs. This tissue is in high demand with some hospitals using five or more a week. These hospitals will store five or ten grafts at a time to avoid not having one when the surgeon requires it. We would recommend the broader interpretation as is listed in the background section.

Finally, regarding the proposed requirement for a "statement of whether each product meets the criteria set out in 1271.10," we interpret FDA's description of this requirement to mean that the agency intends to require only the statement, and not an explanation or summary of why a product does or does not meet the criteria, or, which criteria are not met. (To require such information would be overly burdensome.) It is unclear, however, why FDA has proposed to require this statement or how it will be used by the agency. FDA should clarify the purpose of this proposed requirement.

We thank the agency for the opportunity to comment on the proposal and for its consideration of our views. As FDA proceeds with the establishment of its regulatory fi-amework for human cellular and tissue-based products, we would urge the agency to go slowly, and to impose only those requirements that are truly necessary to address real public health issues.

Respectfully submitted,

Jamie Grooms

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